Journal of Surgical Oncology 1998;67:228–233

Factors Affecting Survival Following Local, Regional, or Distant Recurrence From Localized Melanoma

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Background and Objectives: Approximately one third of all melanoma patients will experience disease recurrence. Factors that affect patient survival following local, regional, or distant first recurrences of localized melanoma are the subject of this investigation.
Methods: Survival times for a total of 1,085 first recurrences from 4,568 localized melanoma patients were examined in relationship to patient and disease factors by Cox regression. Nearly half (48.8%) of all first recurrences were regional, 21.8% were local, and 29.4% were distant recurrences.
Results: Survival following recurrence differed significantly by site of recurrence (local, regional, or distant; $P < 0.0001$). Within each site, the median survival time did not differ by time of recurrence following diagnosis. Significant tumor factors for survival following local recurrence included tumor thickness ($P = 0.0263$) and lesion location ($P < 0.0001$). For regional recurrences, survival was significantly related to ulceration ($P = 0.0105$) and whether the recurrence was combined with a local recurrence ($P = 0.0429$). Survival following distant metastasis was related to number of distant sites ($P < 0.0001$) and whether a visceral site was involved ($P < 0.0001$).
Conclusions: Patient and tumor characteristics predict survival following recurrence. Regardless of disease-free interval, long-term follow-up of melanoma patients is necessary. Patients experiencing distant metastasis have the shortest median survival time compared to patients experiencing local or regional recurrences.
J. Surg. Oncol. 1998;67:228–233. © 1998 Wiley-Liss, Inc.

KEY WORDS: survival analysis; melanoma recurrence; metastatic disease; epidemiology; Cox regression

INTRODUCTION

Approximately one third of all melanoma patients will experience disease recurrence. Factors that predict recurrence have been well described [1]. The prognosis of patients who experience a recurrence depends, in part, on the site of recurrence. Other clinical or pathologic factors that affect survival following recurrence have not been well studied. Whether or not the disease-free interval prior to recurrence is a prognostic factor is controversial. The purpose of this study is to examine prognostic fac-

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Accepted 10 December 1997

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TABLE I. First Recurrence of Localized Melanoma by Site of Recurrence and Time of Recurrence Following Initial Diagnosis*

Site of recurrence	Time of recurrence from initial diagnosis of localized melanoma				Total
	0–2 years	2–5 years	5–10 years	⩾10 years	
Local only	144 (24.2)	64 (19.5)	20 (16.8)	8 (19.5)	236 (21.8)
Regional					
Regional only	299 (50.2)	123 (37.4)	35 (29.4}	14 (34.1)	471 (43.4)
Regional + local	46 (7.7)	8 (2.4)	4 (3.4)	1 (2.4)	59 (5.4)
Distant					
Distant only	76 (12.8)	106 (32.2)	48 (40.3)	13 (31.7)	243 (22.4)
Distant + local	6 (1.0)	3 (0.9)	3 (2.5)	1 (2.4)	13 (1.2)
Distant + regional	22 (3.6)	24 (7.3)	9 (7.6)	4 (9.9)	59 (5.4)
Distant + local + regional	3 (0.5)	1 (0.3)	0 (0.0)	0 (0.0)	4 (0.4)
Total	596 (100.0)	329 (100.0)	119 (100.0)	41 (100.0)	1,085 (100.0)

*Data are presented as n (%).

tors for survival following first recurrences from localized melanoma by time interval of recurrence following diagnosis.

PATIENTS AND METHODS

The patient population utilized for this investigation has been described previously and represents the combined data set of patients treated at the University of Alabama at Birmingham and the Sydney Melanoma Unit in Australia [1]. Among 4,568 patients followed for a median of 5.3 years, 1,085 first recurrences occurred at local, regional, and distant sites.

Statistical Analysis

The Cox proportional hazard model was used as a form of multivariate survival analysis. The dependent variable was time to death, or survival time. In this investigation, the survival time was calculated from the date of first recurrence, not the date of diagnosis. The initial analysis compared survival times stratified by site of recurrence. Cumulative survival rates after recurrence were assessed with the Kaplan-Meier method. The log-rank test from SAS LIFETEST® [2] was utilized to assess equality of curves, and $P < 0.05$ was considered statistically significant. Variables that were statistically significant at $P < 0.05$ were included in the multivariate analysis using with SAS PHREG® [2]. The subsequent analyses developed predictive survival models for each site of recurrence (local, regional, or distant) during varying intervals from initial diagnosis, and over all intervals. The coefficients from these analyses were used to calculate the relative risks (RRs) of mortality, controlling for the other covariates in the models. The RR for each independent variable was computed as the natural logarithm *e* raised to the power specified by the beta coefficient.

Factors examined in the multivariate analysis included clinical factors (site of recurrence, disease-free interval prior to recurrence, age, gender, lesion site, surgical treatment at baseline), and pathologic factors (tumor thickness, Clark's level of invasion, ulceration, growth pattern, metastatic site, and number of metastatic sites). These factors were selected a priori because of their known relationships with melanoma recurrence and survival. Stepwise selection procedures were used for multivariate analyses.

RESULTS

Nearly half (530/1,085, 48.8%) of all patients who experienced recurrences over all time intervals were staged as regional, including regional only and regional plus local. As shown in Table I, 57.9% (345/596) of patients who recurred in the first 2 years experienced regional recurrences. By 5–10 years, most recurrences occurred at distant sites (60/119, 50.4%). Local recurrences were less common among patients who experienced recurrences, comprising less than 25% of all recurrences in each time interval.

Median survival time following recurrence differed significantly by site of recurrence (Fig. 1). Patients with local recurrences had a 5-year survival rate of 41.9%, and a 10-year rate of 33.6%. Patients with regional nodal recurrences had a 5-year survival rate of 36.5% and a 10-year rate of 31.1%. Patients with distant recurrences experienced a dismal survival rate of 11.0% at 5 years and 9.6% at 10 years. The survival for patients who experienced recurrences differed significantly, $P < 0.0001$, by site of recurrence as shown in Figure 1.

There were no significant differences in median survival times by time interval from initial diagnosis of melanoma as seen in Table II. However, when stratified by seven patterns of recurrence, there was a significant difference ($P < 0.0001$) in survival between the patterns (Fig. 2). In fact, the 5-year survival rates for local recur-

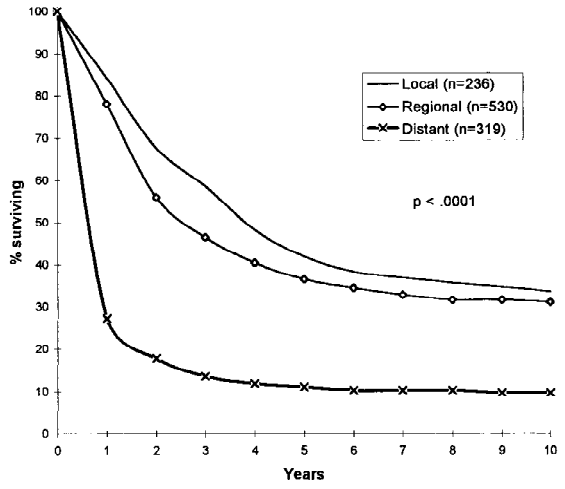

Fig. 1. Survival curves for recurrence from localized melanoma by site of recurrence (log-rank test; significant at $P < 0.05$).

rence only were 41.9%, regional only were 38.3%, but regional plus local disease conferred a poorer survival rate of 22.0% at 5 years. Distant metastasis rates were 11.9% at 5 years, distant plus local 7.7% at 5 years, distant plus regional 9.2% at 5 years, and no patients survived beyond 1 year with distant plus local plus regional recurrences.

The results of multivariate models that examined factors predictive of survival following recurrence are shown in Table III. Age, gender, morphologic diagnosis, Clark's level, and surgical treatment were not significant factors in the analysis. For local recurrences in the first 2 years after initial diagnosis of melanoma, tumor thickness and lesion location were significant factors: Lesions on the trunk or head and neck were associated with a 2.0 increased risk of mortality following recurrence compared to lesions on the extremities ($P = 0.0025$); tumor thickness was significantly related to survival after recurrence during the first 2 years ($P = 0.0258$). At 2–5 years, lesion location was also a significant factor ($P = 0.0257$). The risk of mortality by recurrence-free interval was less than the null value of 1.0 for local recurrences from 0–2 years, suggesting that longer disease-free intervals were associated with lower risk of mortality, but not significantly so ($P > 0.05$).

For regional recurrences within 2 years after initial diagnosis of melanoma, ulceration was a significant factor for predicting mortality after recurrence. Ulcerated lesions were associated with a 40% increased risk of mortality compared to non-ulcerated lesions ($P = 0.0297$). In addition, regional recurrences that occur with local recurrences were significantly associated with mortality (RR = 1.8, $P = 0.0043$). Initial surgical treatment was not significantly associated with survival following recurrence in patients who experienced a regional recurrence ($P = 0.4799$). Only 11.9% (41/345) of the patients with regional recurrences received a prior lymph node dissection.

For regional recurrences that occurred after 2 years of initial diagnosis of melanoma, no factors were significantly associated with survival. As was shown for local recurrences, the risk of mortality in relationship to recurrence-free interval for regional recurrences was also less than 1.0, but not statistically significant ($P > 0.05$). Over all time intervals, 11.3% (60/530) of patients with regional recurrences had received a prior lymph node dissection compared to 470 who did not.

Among patients who experienced distant recurrences within 2 years of initial diagnosis of melanoma, metastasis to non-visceral sites was associated with a lower mortality risk within the first 2 years (RR = 0.4, $P = 0.0004$). In the 2–5-year interval following diagnosis, an increased risk for mortality was found for patients with metastasis to the liver, bone, central nervous system, lung, and abdomen compared to skin. Between 5 to 10 years from diagnosis, only 60 patients experienced a distant metastasis, and there was no statistical difference in survival for those with visceral vs. non-visceral sites. Although over half (51.4%) of all patients who experienced a distant recurrence had undergone a prior node dissection, this initial treatment was not associated with survival after distant recurrence.

If patients who experienced a distant non-visceral metastasis are examined in relationship to those with visceral metastasis, there was a significant difference in survival, as expected (Fig. 3). Among patients with distant metastasis, those with non-visceral metastasis had a 6-month survival of 56% compared to 42% for patients with metastasis to other sites, including abdomen/pelvis, bone, liver, central nervous system, and lung. At 1 year the survival rate for non-visceral sites was 41% compared to only 19% for visceral sites. The predominant metastatic site in the first 2 years was skin (41.1% of the patients), in years 2–5 the predominant site was lung (43.3%), and in years 5–10 the predominant sites were lung (53.3%) and central nervous system (33.3%).

The number of metastatic sites was significantly related to survival from distant metastasis. Each additional site was associated with an 80% increased risk of mortality (RR = 1.8, $P = 0.0001$). For one site the 6-month survival rate was 55.6% and the 1-year survival rate was 37.7%. For two sites the 6-month survival rate was 26.2% and at 1 year it was 14.6%. For three sites the 6-month survival rate was 18.1%, and it was only 9.1% at 1 year. For four sites all patients were dead by 4 months and for five sites all patients were dead by 1 month. The median survival was 7.2 months for one site and only 1 month for five sites.

TABLE II. Median Survival Time in Months of Recurrent Melanoma by Site of Recurrence and Time From Initial Diagnosis of Localized Melanoma

	Time of recurrence from initial diagnosis of localized melanoma			
Site of recurrence	Overall	0–2 years	2–5 years	5–10 years
Local only (n = 236)	43	41	42	>61
Regional (n = 530)	30	25	35	34
Distant (n = 319)	6	5	6	6

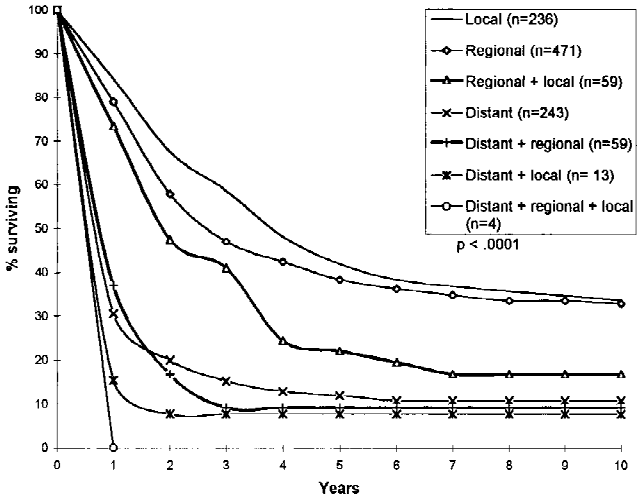

Fig. 2. Survival curves for recurrence from localized melanoma by pattern of recurrence (log-rank test; significant at $P < 0.05$).

DISCUSSION

This investigation showed that specific patient and tumor factors at diagnosis are associated with survival following recurrence from localized melanoma. For patients who experience local recurrences, tumor thickness and lesion location were significantly related to survival after recurrence. Ulceration and whether a regional recurrence occurs with a local recurrence are significant factors for survival for patients with regional recurrences. Among patients who experience distant recurrences, site of metastasis and number of distant sites are significant prognostic factors for survival following distant recurrence. Initial surgical treatment at baseline diagnosis was not a significant factor for survival following disease recurrence for patients within any subgroup.

The survival rates by site of recurrence in this study are similar to those reported in a review paper by Buzell and Zitelli [3]. The weighted average survival rates following regional recurrence reported by Buzell and Zitelli [3] were 37% at 5 years and 32% at 10 years. The results of our study were 36.5% at 5 years and 31.1% at 10 years. Similarly, our median survival time of 6 months following distant recurrence compares with other reports. We found a median survival time of 9.6 months for non-visceral metastatic lesions and 4.8 months for visceral metastatic lesions. A weighted average of 8 months for non-visceral lesions and 4.7 months for visceral lesions has been reported in a review paper [3], and has been noted by Gadd and Coit [4].

In our analysis, the total number of distant metastatic sites for patients with distant metastases ranged from 1 to 5: 229/319 (71.8%) had only one distant site, 71 (22.3%) had two sites, 11 (3.4%) had three sites, 7 (2.2%) had four sites, and only one patient (0.3%) had five sites. The number of metastatic sites was a predominant prognostic variable, as has been reported by Balch et al. [5].

The site of distant metastasis was a factor for survival for patients experiencing recurrences up to 5 years; metastasis to visceral sites had the greatest mortality risk. Patients who experienced a non-visceral metastasis had a better survival compared to patients who did not have a non-visceral metastasis. However, the inverse relationship between non-visceral metastasis and disease mortality was not significant for patients who had a distant metastasis 5 years or more after diagnosis.

This analysis did not find a relationship between disease-free interval and survival following recurrence. Although the risk estimates suggest a lower mortality is associated with a longer disease-free interval, the relationship is not significant. Categorization of the disease-free interval with cutpoints did not result in a significant relationship. It is possible that the relationship between recurrence-free interval and survival following recurrence is confounded by whether the follow-up is physician or patient directed.

Crowley and Seigler [6] reported that the relationship between disease-free interval and subsequent survival was only a predictive variable for those patients who had very early (<1.0 year) or very late (>10.0 years) recurrences. They reported that for the majority of the patients, the disease-free interval did not predict subsequent survival. The work of Crowley and Seigler [6] suggests that once the steady state between tumor and host is disturbed, disease progression occurs at a rate that is independent of the duration of tumor dormancy.

Reintgen et al. [7] reported that tumor thickness, ulceration, lesion site, age, and disease-free interval were important factors influencing survival following recurrence. In the report of Reintgen et al. [7], the disease-free interval was not examined by patterns of recurrence, and

TABLE III. Multivariate Analysis of Survival Following Recurrence From Localized Melanoma by Patient Site of Recurrence and Time of Recurrence From Initial Diagnosis of Localized Melanoma

	Relative risk (*P*)*				
Time of recurrence	0–2 years	2–5 years	5–10 years	>10 years	Overall
Local	n = 144	n = 64	n = 20	n = 8	n = 236
	censored = 65	censored = 33	censored = 14	censored = 6	censored = 118
Tumor thickness[a]	1.2 (0.0258)	1.0 (0.8698)	—[d]	—[d]	1.2 (0.0263)
Axial vs. extremity	2.0 (0.0025)	2.4 (0.0257)	—[d]	—[d]	2.1 (<0.0001)
Recurrence-free interval	0.7 (0.1420)	1.3 (0.3435)	—[d]	—[d]	0.9 (0.0634)
Lymph node dissection vs. wide local excision	0.9 (0.6669)	0.9 (0.6996)	—[d]	—[d]	0.9 (0.4443)
Regional	n = 345	n = 131	n = 39	n = 15	n = 530
	censored = 140	censored = 56	censored = 18	censored = 11	censored = 225
Tumor thickness	1.0 (0.5207)	1.0 (0.5846)	1.1 (0.6685)	—[d]	1.0 (0.2595)
Ulcerated vs. non-ulcerated	1.4 (0.0297)	1.4 (0.1948)	0.4 (0.2381)	—[d]	1.5 (0.0105)
Regional plus local vs. regional only	1.8 (0.0043)	0.8 (0.6154)	0.6 (0.4231)	—[d]	1.5 (0.0429)
Recurrence-free interval	0.8 (0.1017)	0.9 (0.5138)	1.1 (0.4596)	—[d]	0.9 (0.1026)
Lymph node dissection vs. wide local excision	1.2 (0.4799)	1.3 (0.5272)	0.2 (0.0798)	—[d]	1.0 (0.9748)
Distant	n = 107	n = 134	n = 60	n = 18	n = 319
	censored = 20	censored = 13	censored = 7	censored = 3	censored = 43
No. of distant sites[b]	1.5 (0.0611)	2.0 (0.0001)	1.9 (0.0005)	—[d]	1.8 (<0.0001)
Non-visceral vs. visceral sites[c]	0.4 (0.0004)	0.6 (0.0021)	1.0 (0.9305)	—[d]	0.6 (<0.0001)
Recurrence-free interval	1.0 (0.8548)	0.9 (0.6814)	0.9 (0.2114)	—[d]	0.9 (0.2997)
Lymph node dissection vs. wide local excision	1.3 (0.2251)	0.9 (0.8296)	1.0 (0.9917)	—[d]	1.0 (0.4774)

*$P < 0.05$ is considered statistically significant for each factor (Wald test).
[a]Coded as follows: 1 = <0.76 mm, 2 = 0.76–1.49 mm, 3 = 1.50–2.49 mm, 4 = 2.50–3.99 mm, 5 = 4.00–7.99 mm, 6 = ⩾8.00 mm.
[b]Number of sites = 1–5.
[c]Visceral sites include abdomen/pelvis, lung, liver, central nervous system, and bone.
[d]Insufficient numbers for statistical computations.

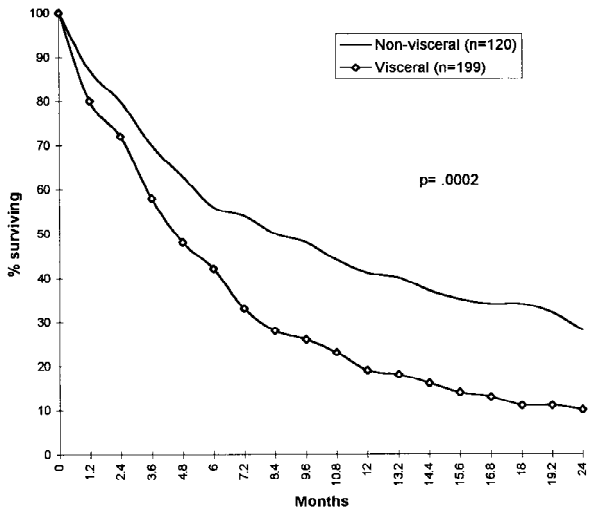

Fig. 3. Survival curves for distant recurrences from localized melanoma for patients with visceral vs. non-visceral recurrences (log-rank test; significant at $P < 0.05$).

they found no relationship between survival in those patients that recurred locally vs. those with melanoma that recurred regionally. Our risk ratio (0.9) for recurrence-free interval was similar to that reported by Reintgen et al. [7], who reported a risk estimate of 0.80 ($\exp^{-0.236}$) for number of disease-free years prior to recurrence.

This investigation was conducted retrospectively, and information on treatment following disease recurrence was not available for all recurrences. Treatments for local and regional disease recurrences, if available, may have influenced our model estimates, although there were not any effective treatments for disease recurrence for patients in our population. Interferon (IFN) α-2b, which has been reported to show a significant benefit in the relapse-free and overall survival of high-risk melanoma patients, was not available to patients in our study [8]. Other factors might also be important for predicting survival, such as the number of involved nodes in patients with regional recurrence [3]. A decrease in survival has been observed as the number of involved nodes increases. Unfortunately, data on this variable were not available in this investigation.

The estimates in Table III should be interpreted in conjunction with the accompanying *P*-values. Because four models were tested for each patient disease stage of recurrence, the number of hypothesis tests should be taken into account when interpreting the *P*-values. For conservative interpretation of results, $\alpha = 0.05/20 = 0.0025$ might be utilized to judge the statistical signifi-

cance of the results, even though the models were applied to independent patient populations.

CONCLUSIONS

Regardless of the disease-free interval, lifetime follow-up of melanoma patients is necessary because a complete cure can never be assumed [9]. Because over 50% of all relapses occurred within 2 years, this emphasizes the need to concentrate follow-up in the early time periods following diagnosis. This analysis found several factors that predict survival following a relapse from localized melanoma. Site of disease recurrence was significantly associated with survival. Tumor thickness and lesion location were significant factors following localized recurrence. Prognostic factors following regional recurrence included tumor ulceration and whether the regional recurrence was combined with a local recurrence. The prognosis for patients experiencing distant metastasis was poor, and significant factors for survival included site of metastasis and number of metastatic sites. Because the clinical behavior of melanoma is variable, the prognostic factors discussed in this paper are useful predictors of survival following recurrence.

ACKNOWLEDGMENTS

The authors thank Ms. Linda Austin for assistance with data management.

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